

12

**EUROPEAN PATENT APPLICATION**

21 Application number: 87850240.0

51 Int. Cl.<sup>4</sup>: **A 61 K 31/19**  
**A 61 K 9/02**

22 Date of filing: 06.08.87

30 Priority: 07.08.86 SE 8603338

43 Date of publication of application:  
24.02.88 Bulletin 88/08

84 Designated Contracting States:  
BE DE FR GB LU NL SE

71 Applicant: Andersch, Björn  
Elkedal 2630  
S-430 40 Särö (SE)

72 Inventor: Andersch, Björn  
Elkedal 2630  
S-430 40 Särö (SE)

74 Representative: Mossmark, Anders et al  
Patentbyran WEST-PATENT AB Stora Nygatan 15  
S-411 08 Göteborg (SE)

54 Agent for treating conditions in the vagina.

57 Cream, gel or vaginal suppository for treating conditions in the vagina and containing lactic acid with buffered substance, the content being such that the pH lies within the range from 3.5 to 4, preferably close to 3.8. The agent contains a growth substrate for lactic acid bacteria and, moreover, a vehicle which confers consistency and is of a type which is inert in this connection.

**EP 0 257 007 A1**

## Description

Agent for treating conditions in the vagina

The present invention relates to an agent for treating conditions in the vagina according to the preamble of patent claim 1.

It is known that an acid environment in the vagina of a woman is of crucial importance for protection against infection. This acid environment is maintained by a lactobacterial flora which produces lactic acid. In order for this production of lactic acid to be maintained, to provide the pH reduction necessary for protection against infection, a favourable environment is needed for the bacterial flora.

A favourable environment of this type is generally present and results in a pH of approximately 4 in the mucous membrane secretions. However, the environment can be disturbed by factors such as variations in the oestrogen concentration during certain periods of the menstrual cycle and during the menopause and also by an increasing occurrence of secretions of various types, for example from protracted menstrual haemorrhages, premenstrual bloody discharges, mid-cycle bleeding and ejaculate. Foreign bodies in the vagina, for example coils, pessaries and those inserted, for example, in connection with antibiotic treatment and on washing can also lead to a disruption of the bacterial flora which is such that the pH rises. When the pH rises above 4.5 there is an increased tendency towards growth of anaerobic bacteria. Disruptions of the bacterial flora in the vagina without inflammatory reactions in the mucous membrane are referred to as vaginosis (NSV) and lead to offensive discharges and pH's over 4.5, but they are not generally regarded as an actual disorder. However, vaginosis is an indication that the defence against infection, which defence depends on a low pH, has been weakened and, in unfavourable circumstances, this leads to actual infection.

It is known to use agents in an attempt to cure infections by seeking to re-establish an acid environment in the vagina by supplying lactic acid. In this connection the first aim has been to create an acid environment and to counterbalance the more alkaline environment by artificial supply of lactic acid. On the basis of this assumption, attempts were therefore made to use extraneous sources to replace the lactic acid no longer provided to a sufficient extent by the bacterial flora in the vagina. In this connection agents were used which destroyed the lactic acid production which was dependent on environment. Moreover, in many cases substances were supplied such as preservatives for the product and agents intended to inhibit growth of pathogenic bacteria in the vagina, which agents were of a type which further impaired the environment for lactobacteria. This created a condition in which the natural mechanism with symbiosis between bacterial flora and tissue was lost. This is particularly unfortunate when those products are used for treatment of vaginosis which cannot be regarded as an actual disorder in itself, but which can result in such a disorder or in a chronic abnormal

condition when agents are supplied which were intended to act as medicaments but which make it difficult to re-establish the natural advantageous environment.

The object of the present invention is to produce an agent for treating conditions in the vagina, which agent reinforces the natural protection mechanisms by helping to re-establish the productive environment for the lactobacteria, so that, after short-term use of the agent, the natural mechanism for protection against infection is re-established.

The object of the invention is achieved by means of an agent according to the characterizing part of patent claim 1.

The agent according to the invention has a cream or gel consistency or is given the form of a vaginal suppository. The agent contains as its main constituents:

Lactic acid supplemented (buffered) with sodium hydroxide to give a pH of 3-4. The pH is advantageously close to 4 and is not so low that the acid irritates the tissues or impairs the environment for the lactobacteria which require a moderately acid environment. A pH of 3.7-3.8 has been shown to be particularly advantageous.

A growth substrate for the lactobacteria, so that treatment not only results in adjustment of the pH level to a lower figure by means of supplying lactic acid but also to re-establishment of an advantageous environment for the growth of the lactobacteria in order to regenerate the natural conditions. Glycogen and lactose are suitable growth substrates.

A vehicle for the active constituents of the agent. One such suitable vehicle for a cream is propylene glycol, but other substances of an inert nature are also known to be of use in this connection as vehicles.

Consistency agent such as, in the case of creams and gels, methyl hydroxypropyl ether of cellulose. As an example of a commercial product there may be mentioned Hypromellose<sup>®</sup> 90 HG 4000.

If a vaginal suppository is to be produced, a vehicle is required which makes it possible to form an article which is relatively solid at room temperature and in a dry environment, but which melts at body temperature and in contact with body fluid. In this connection there may be used polyethylene glycol, PEG, which gradually melts in the vaginal environment.

A more specific composition emerges from the following examples.

Agent according to the invention:

Example 1. Cream

Lactic acid 5.0 g  
Na OH ad. pH 3.9  
Glycogen 0.1 g  
Propylene glycol (85%, remainder H<sub>2</sub>O) 15.0 g  
Hypromellose<sup>®</sup> 90 HG 4000 (2.5%, remainder H<sub>2</sub>O) ad. 100 g

Example 2. Cream

Lactic acid 5.0 g  
Na OH (5M) 4.1 g  
Glycogen 0.1 g  
Propylene glycol (85%, remainder H<sub>2</sub>O) 15.0 g  
Hypromellose<sup>®</sup> 90 HG 4000 (2.5%, remainder H<sub>2</sub>O) ad. 100.0 g

Example 3. Vaginal suppository

Method of production.

I. Dissolve 19.94 g Na OH (pastilles) in 146.06 g lactic acid solution.

II. Dissolve 600 g PEG 4000 in 900 g PEG 600 (warming cabinet, 60°C).

III. Dissolve 2.776 g Lactose in a minimal amount of water.

IV. Take solution I and solution III, mix into solution II with stirring to give a homogeneous mixture. Store mixture IV in the warming cabinet at 60°C.

The actual casting of the vaginal suppositories is carried out most expediently in this manner in a moulding body. The moulding body should stand in the cold (for example -18°C). The mould is brought to room temperature, 21°C, and mixture IV is poured into the mould. When the mixture sets (is reduced in volume) the mould is gradually filled and the excess is finally removed to give the desired article. It is important not to compress and pack together the agent in the mould since a softer vaginal suppository is then obtained. If the solution is allowed to set without mechanical action, the finished article is easy to remove.

The content is thus per 100 g:

Lactic acid solution 8.752 g  
Na OH 1.195 g  
Lactose 0.166 g  
PEG 4000 35.954 g  
PEG 600 53.930 g

Comparison test

The object was to investigate the effects of various cream compositions on the growth of lactobacteria and also other bacteria generally present in the vagina, such as *Staphylococcus aureus*, *Pseudomonas*, *Candida albicans*, *Clostridia*, *E.coli* and enterococci.

Agents, which are not the subject of the invention and are previously known, are given for comparison:

a. Lactic acid 5.0 g

Na OH, ad. pH 3.9

Propylene glycol (85%, remainder H<sub>2</sub>O) 15.0 g

Hypromellose<sup>®</sup> 90 HG 4000 (2.5%, remainder H<sub>2</sub>O) ad. 100 g

b. Lactic acid 5.0 g

Na OH, ad. pH 3.5

Propylene glycol (85%, remainder H<sub>2</sub>O) 15.0 g

Hypromellose<sup>®</sup> 90 HG 4000 (2.5%, remainder H<sub>2</sub>O) ad. 100 g

c. Conc. acetic acid 920 mg

Ricinoleic acid 50 mg

Sulph. oxyquinoline 25 mg

Glycerol, gum arabic

Potassium hydroxide

Egg albumen mix

Tragacanth

Preservative (propyl parahydroxybenz., stannous chloride)

Odorant

Aq. purif. q.s. - pH 4.0

The following bacteria were tested

The initial bacteria count was  $1 \times 10^9$ . *Staph. aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, *Clostr. sporogenes*, EF-15941, *Lactobacillaceae* var. *rhamnosus*, EF 18011, *E.coli*, *Enterococcus-spec.* 9739.

0.5 g of the various cream compositions was placed in sterile plastic tubes. The bacteria species were suspended in physiological saline solution at a rate of  $1 \times 10^9$ /ml. 0.5 ml of the suspension was transferred to the various cream compositions and then thoroughly shaken in a mixer. It was then cultured directly onto agar plates. The plates were then placed in a thermostat at 37° for 1-2 days, after which a reading was taken. Culturing onto the plates was carried out directly in part and then after 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 7 hours, 8 hours, 10 hours, 12 hours, 16 hours, and then each day.

Result

The table shows that there was no great difference between lactic acid creams without glycogen at a pH of 3.5 compared with a pH level of 3.9 in respect of the time taken for all the bacteria tested in the study to be killed:

The content of preservative (in agent c) provided for a more rapid killing of lactobacteria than creams which did not contain any preservatives. The lactobacteria survived twice as long if the lactic acid cream contained 0.5 g glycogen than if it contained no glycogen.

*E.coli* survived considerably longer in agent c compared with the three lactic acid creams. *Staph. aureus* and *Pseudomonas aeruginosa* did not survive any longer than six hours in any of the creams. On the other hand, there was no effect on the growth of *Candida albicans* and *Clostr. sporogenes*.

This shows that it is of great importance for the balance between the microorganisms in the vagina to be maintained. Above all it is important that the lactic acid bacteria are allowed to predominate in the

vaginal content, since these bacteria confer a natural protection against infection by virtue of their ability to form lactic acid and thereby acidify the vaginal content.

In the study mentioned various cream compositions were tested in respect of the survival of the lactic acid bacteria in vitro in addition to other bacteria which are generally present but which have pathogenic properties. It emerged from the study that preservatives in the cream do not favour the growth of the lactobacteria. After only 1 hour all lactobacteria in agent c were killed. In the creams which contained only lactic acid, the lactobacteria survived considerably longer and, in addition, longer in creams with the lowest pH. On addition of 0.1 g glycogen, the lactobacteria survived twice as long compared with the creams which contained only lactic acid.

The situation as regards the effects of the various creams on the composition of the bacterial flora in vivo is of course different. The pH in a lactic acid cream should be set lower than the Pka value for lactic acid (pH = 3.87) in order to better withstand the expected alkaline charge. In accordance with the abovementioned results, the pH of a cream for treating vaginosis should be set somewhat lower than 3.8 by the addition of glycogen. Glycogen is found in abundance in the vaginal epithelial cells in fertile women and is an important nutrient substrate for the lactobacteria. In addition, the cream should not contain any preservatives. The requirements for creams made without preservatives are of course that undesired bacteria do not grow in the cream tubes during storage. Storage tests on the abovementioned lactic acid creams showed that after 16 weeks of storage there was no fungal growth or bacterial growth.

In the treatment of vaginosis (offensive discharges caused by imbalance in the vaginal flora without inflammation) it is important to re-establish the lactobacterial flora. For this purpose the invention has provided an acidic lactic acid cream containing glycogen without preservatives. Compared with creams which contain only lactic acid (agents a and b) or acidic creams with preservatives (agent c) the cream according to the invention has been shown in vitro to have twice as favourable an effect on the survival of the lactobacteria. The agent according to the invention can thus be used for reestablishing a normal environment in cases of vaginosis, whereas previously known agents lead to a risk of the lactic acid production being lost. Intestinal bacteria and Staph. aureus have not survived for more than 4 and 6 hours respectively in the cream according to the invention.

#### Claims

1. Agent for treating conditions in the vagina in the form of a cream, a gel or vaginal suppository and containing lactic acid with buffering substance, characterized in that the content of lactic acid and buffering substance is

such that the pH lies within the range from 3.5 to 4, preferably close to 3.8, in that the agent contains a growth substrate for lactic acid bacteria and, moreover in a manner known per se vehicles which are of a type which is inert in this connection and which form a cream- or gel-like consistency or, alternatively, a substance which melts at body temperature and in body fluid.

2. Agent according to Claim 1, characterized in that the lactic acid is incorporated in a considerably greater weight proportion than the growth substrate, for example in weight ratios of 20:1 down to 500:1.

3. Agent according to Claim 2, characterized in that the lactic acid and the growth substrate are incorporated in weight ratios of approximately 50:1.

4. Agent according to one of Claims 1 to 3, characterized in that the growth substrate is comprised of glycogen.

5. Agent according to one of Claims 1 to 3, characterized in that the growth substrate is comprised of lactose.

6. Agent according to Claim 4, characterized in that its content is essentially as follows:

Lactic acid 5.0 g  
Na OH for buffering the lactic acid to a pH of essentially 3.7-3.8  
Glycogen 0.1 g  
Propylene glycol (85%, remainder H<sub>2</sub>O) 15.0 g  
Consistency agent such as methyl hydroxypropyl ether of cellulose ad. 100 g

7. Agent according to Claim 4, characterized in that its content is essentially as follows:

Lactic acid 5.0 g  
Na OH (5M) 4.1 g  
Glycogen 0.1 g  
Propylene glycol (85%, remainder H<sub>2</sub>O) 15.0 g  
Hypromellose® 90 HG 4000 (2.5%, remainder H<sub>2</sub>O) ad. 100 g

8. Agent in the form of a vaginal suppository and according to Claim 5, characterized in that its content is essentially as follows:

Lactic acid 8.752 g  
Na OH 1.195 g  
Lactose 0.166 g  
PEG 4000 35.954 g  
PEG 600 53.930 g



European Patent  
Office

# EUROPEAN SEARCH REPORT

Application Number

EP 87 85 0240

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
X	GB-A- 272 543 (A. BOEHRINGER) * Page 1, line 46 - page 2, line 15; claims 1-4 *	1,4,5	A 61 K 31/19 A 61 K 9/02
Y	----	2,3,6-8	
X	GB-A- 253 918 (A. BOEHRINGER) * Page 2, lines 32-109; claims 1-7 *	1,4,5	
Y	----	2,3,6-8	
X,P	CHEMICAL ABSTRACTS, vol. 105, 1986, page 396, abstract no. 49063y, Columbus, Ohio, US; & HU-A-37 565 (E. MEHESZ et al.) 23-01-1986 * Abstract *	1,5	
Y,P	Idem ----	2,3,6-8	
Y	GB-A-2 112 285 (INSTITUTO FARMACOLOGICO SERONO S.p.A.) * Page 1, line 26 - page 2, line 19; claims 1-13 *	1-8	
Y	DE-A-3 303 018 (K. MEINEN) * Whole document *	1-8	
	-----		
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	01-12-1987	TZSCHOPPE, D.A.	
<b>CATEGORY OF CITED DOCUMENTS</b>			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			